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# Abstract and Review of "Zur Erbpathologie der Schizophrenie" (Contribution to the Genetics of Schizophrenia)*

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**Starting from the 722 probands originally studied by Rüdin, Bruno Schulz re-examined them and their relatives confirming the diagnosis in 660. While Rüdin sought for mendelian ratios in siblings, Schulz, anticipating modern methods, focused on the family study method as an approach to clarifying possible etiologic heterogeneity within the schizophrenia syndrome. Using a Kraepelian approach to diagnosis, Schulz reports a MR for narrowly and broadly defined schizophrenia of 6.7 and 8.2% in siblings and 2.6 and 3.7% in parents. He found no evidence for a difference in risk of illness in siblings as a function of either the gender or outcome of the proband. The risk for schizophrenia was significantly increased in siblings of hebephrenic probands. Compared to siblings of probands with no identified factor which precipitated their schizophrenia, the risk for schizophrenia was significantly decreased in probands with a physical etiologic factor but did not differ in siblings of probands with a psychological etiologic factor. The risk for schizophrenia was particularly low in siblings of probands whose onset of illness occurred within a year of major head trauma.**



**KEY WORDS: psychiatry, history, psychiatric genetics, schizophrenia**

## METHODS

The probands in this study were the 722 cases of schizophrenia collected by Rüdin in the Psychiatric Clinic at the University of Munich and formed the basis of Rüdin's monograph [1916]. As outlined in our review of that work, it appears that this series was one of consecutive admissions with a "certain" diagnosis of dementia praecox to the Munich Psychiatric University Clinic (from 1904 to probably 1913), and from its predecessor, the Psychiatric Department of the Hospital Left River of Isar (from 1898 to 1904) as well as a small number of cases from the Eglfing Hospital. Schulz used only the 722 cases from the University Psychiatric Hospital and its predecessor. Twenty cases were lost due to disappearance of records, lack of adequate information or the inability to trace the family.

These 702 probands were re-diagnosed by Schulz and colleagues on the basis of case summaries and follow-up information. Schulz writes

> In only a very few cases did further inquiry seem unnecessary. Aside from these cases, I collected new information on all cases included in this study, on the outcome of all probands alive at the conclusion of Rüdin's study and their siblings, parents and other relatives considered in that study (p. 196).

Schulz's diagnostic review was "blind" in that names had been removed and substituted with numbers. Forty-two further cases were excluded as uncertain schizophrenia, leaving 660 probands, 367 male and 293 female. At the time of his investigation, 293 (44.4%) of the sample was dead.

Schulz discusses diagnostic approaches to schizophrenia for nearly 20 pages (pp. 175–195), comparing the approaches of several leading psychiatrists. He concludes by accepting Kraepelin's approach, which is available in English translations of three editions of his famous textbook [Kraepelin, 1904, 1907, 1971]. In addition, all the initial probands in Rüdin's series had been considered to be definitely schizophrenic by Kraepelin and Rüdin 20 years earlier. Schulz eliminated 42 additional probands as diagnostically uncertain because follow-up information cast doubt on the original

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As this paper abstracts, reanalyzes and interprets the original article by B. Schulz, it is not a translation, and hence B. Schulz's name is not listed as author.

**Zeitschrift für die gesamte Neurologie und Psychiatrie* 143:175–293, 1932, by Bruno Schulz.

diagnosis. His comments on the cause for exclusion are illuminating with regard to his diagnostic approach:

> [Cases]...were excluded...exclusively because of their clinical picture and therefore many recovered cases are among them. However, recovery by itself was not decisive for exclusion...(p. 196). These cases were excluded...because when considering the clinical picture, I judged the diagnosis of schizophrenia to be uncertain or even wrong (p. 259).

It would appear that Schulz's diagnostic view of schizophrenia was narrow. This is exemplified by the fact that one sibling with paranoia was not considered even an uncertain case of schizophrenia.

More detail is provided on the criteria Schulz used for subtyping schizophrenia. Furthermore, 75 brief case histories are provided in the appendix. Schulz formed three "pure" and four "mixed" subtype groups. He found subtyping to be difficult because he had to rely on reports and case histories rather than direct clinical observation. He particularly stated that some of his subtype assignments might be questionable. The criteria provided for the "pure" subtypes were

> "simple hebephrenia"—presence of blunt and inadequate affect and/or foolish behavior and the absence of prominent catatonic symptoms, delusions (except delusions of reference and simple nonbizarre somatic delusions) and vivid hallucinations.
>
> catatonia—presence of stupor, echopraxia, flexibilitas cerea, and/or catalepsy in the absence of delusions.
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> dementia paranoides—delusions dominate the clinical picture in the absence of prominent hebephrenic and/or catatonic features.

Schulz formed four "mixed" subtype groups: paranoid-hebephrenic, hebephrenic-catatonic, paranoid-catatonic, and other. He classified nearly twice as many probands as mixed (n = 430) than as pure subtypes (n = 230).

The diagnostic approach to relatives was similar to that used in probands, with the major exception that Schulz categorized secondary cases as either definite or uncertain schizophrenia. When diagnosing secondary cases, neither Schulz nor his colleagues knew to which family they belonged. Therefore, although there was no normal control group, this was a "blind" study with respect to the subtype and other clinical features of the probands.

Schulz used multiple sources of information on both probands and siblings. These included i) case histories and records which contained information collected on this series by Hoffman [1921] and I. Weinberg [1928], ii) personal visits to at least one member of each family and, where possible, to as many members as could be seen, and iii) information from local authorities such as priests, mayors, teachers, friends, and neighbors. In only a few cases (number not given), Schulz was unable to contact any family members.

Schulz was well aware of the methodologic problems associated with age-correction. He predominantly used the Abridged Weinberg method with an age at risk of 16–40. However, he also applied a more precise method (the Strömgren method had not yet been published) that assumed a linear increase in cumulative risk over the age period 16 to 40. This method resulted in modestly larger morbid risks, but the differences were small.

The risk for schizophrenia in the general population of 0.85% was obtained from studies of the siblings and parents of three proband groups which came from the same general population as the schizophrenic probands: i) individuals with dementia [Schulz, 1927], ii) spouses of hospital patients [Schulz, 1931], and iii) spouses of patients with general paralysis [Luxenburger, 1928].

Schulz was particularly interested in using the "family method" to detect potential heterogeneity within the schizophrenic syndrome. Therefore, in addition to subtype, he classified the probands in the following additional ways:

> Outcome 10+ years after admission: Schulz presents a complex system of nine outcome categories. For our purposes, we will use the following five categories: recovered (67 or 10%), mild defect (32 or 5%), remitting course (55 or 8%), severe defect (347 or 53%), and dead (159 or 24%). The deceased group appeared to be very heterogeneous, and not very informative with regard to outcome.
>
> Precipitating factors: these were classified as either absent (n = 340), or present (n = 320), and if present divided into the following categories: possible (literally "improbable") psychological causes such as unhappy love affair, harsh job conditions, and stay in a foreign country; possible somatic causes such as fall on head in childhood without obvious sequelae, and infectious diseases many years before the onset of schizophrenia; probable psychologic factors such as traumatic break-up of romantic relationship or a prison sentence and probable somatic factors such as head injury immediately before the onset of schizophrenia, or onset during pregnancy or the immediate post-natal period.
>
> Premorbid personality: normal or not normal.

As in Rüdin's original sample, several sibships must have contained more than one proband. Although not specifically stated, we assume, given Schulz's methodologic sophistication, that Weinberg's proband method was used.

In other introductory remarks in this monograph, Schulz discussed a number of important questions in the genetics of schizophrenia including i) is schizophrenia an appropriate "unit" for genetic analysis?, ii) are there any subgroups of schizophrenia which might show a classic "monogenic" mode of inheritance?, iii) are psychological processes more useful than "superficial" clinical symptoms and signs at identifying a hereditary core group of patients?, and iv) do the classic clinical subtypes of hebephrenia, catatonia, and dementia paranoides show genetic differences?

## RESULTS

### Morbid Risk (MR) in Siblings

The total number of siblings of probands examined is not given, but the lifetimes at risk using the Abridged

Weinberg (AW) method was 1,959.5 (male 970.5, female 989). One can calculate that Schulz must have identified 131 definite and 30 uncertain cases of schizophrenia in the siblings, for MRs of 6.69 ± 0.56 and 8.22 ± 0.62%, respectively, for definite and definite + uncertain schizophrenia.

### Morbid Risk in Parents

The total 1,320 parents of the probands produced 1,277.5 lifetimes at risk for schizophrenia. Schulz identified 33 definite and 14 uncertain cases of schizophrenia in parents for MRs of 2.58 ± 0.44 and 3.68 ± 0.53% for definite and definite + uncertain schizophrenia, respectively.

### Morbid Risk by Sex

No significant difference was found in the risk for definite schizophrenia in the siblings of male vs. female probands (6.3 vs. 6.4%, respectively) ($\chi^2$ = 0.00, NS), nor in the risk in male vs. female siblings (6.3 vs. 7.0%, respectively) ($\chi^2$ = 0.37, NS).

There is a modest excess of same-sex pairs of schizophrenic probands and siblings, which for definite schizophrenia is male-male 37, female-female 38, and male-female 56. Because we do not know the specific sex distribution of siblings as a function of the sex of the proband, the best we can do is test random association, which gives expected values for these three types of pairs of 32.2, 33.2, and 65.5, respectively. However, by a $\chi^2$ goodness-of-fit test, the observed and expected do not differ significantly ($\chi^2$ = 2.79, df = 2, NS). Including uncertain cases of schizophrenia, the evidence for homotypia by sex is even less marked ($\chi^2$ = 2.61, df = 2, NS).

### Morbid Risk by Subtype

The risk for schizophrenia in siblings differed significantly by subtype of the proband ($\chi^2$ = 14.43, df = 6, $P$ = .025). Nearly all of this effect stemmed from the high risk found in the small sample of siblings of hebephrenic probands (13/66.5 = 19.5 ± 4.9%). The risks in the siblings of the other groups, ranging from 5.6 to 9.4%, do not differ significantly from one another ($\chi^2$ = 2.94, df = 5, NS). The risk in siblings of the other two "pure" proband subtypes was catatonic, 7.4 ± 1.4 and paranoid, 7.0 ± 1.8%.

### Subtype Concordance in Affected Sib Pairs

Schulz presents the subtypes of 131 proband-sibling pairs. Including individuals diagnosed as the "other" subtype (n = 131), there is no significant concordance for subtype in these affected sib pairs (kappa = + 0.03 ± 0.04, NS). Excluding pairs where the proband and/or sibling were considered "other," the concordance among the remaining "pure" and "mixed" pairs (n = 76) increases, but still does not reach statistical significance (kappa = +0.11 ± 0.06, NS). Including only the small number of pairs where both proband and sibling had a "pure" subtype diagnosis (n = 14), concordance for subtype becomes substantial and significant (kappa = +0.58 ± 0.22, $P$ = .007).

### Morbid Risk by Outcome of Proband

The MR (±SE) for definite plus uncertain schizophrenia in the siblings of the four living outcome groups were: recovered, 5.4 ± 1.8%; mild defect, 10.8 ± 3.0%; remitting course, 7.8 ± 2.1%; and severe defect, 8.4 ± 0.8%. These risks do not differ significantly from one another ($\chi^2$ = 2.64, df = 3, NS), although the risk in siblings of the recovered group is substantially lower than in the siblings of the three remaining proband outcome groups. Interestingly, the risk of illness was highest in the siblings of the deceased probands (10.0 ± 1.4%), but this was not significantly greater than in the siblings of living probands (8.3 ± 0.7%, $\chi^2$ = 1.45, df = 1, NS).

### Concordance in Outcome in Affected Sibling Pairs

Schulz cross-classified outcome in 68 proband-sibling pairs where the proband was alive. Although he commented on an apparent association, especially a higher probability of good outcome in affected siblings of good outcome probands, using the four proposed outcome categories, no statistically significant resemblance was found in outcome in these pairs (kappa = +0.02 ± 0.12, NS).

### Morbid Risk by Precipitating Factor in Proband

The risk for definite + uncertain schizophrenia in the siblings of the five different groups of probands classified as to precipitating factor by Schulz were as follows: none (called by Schulz the "endogenous group"), 10.0 ± 1.0%; possible psychological cause, 7.0 ± 1.4%; probable psychological cause, 3.1 ± 3.1%; possible physical cause, 4.3 ± 1.1%; and probable physical cause, 3.4 ± 1.2%. Compared to siblings of the endogenous group, neither siblings of probands with a possible nor those with a probable psychological cause had a significantly different risk for schizophrenia ($\chi^2$ = 2.65 and 1.68, respectively, NS). By contrast, siblings of probands with either a possible ($\chi^2$ = 11.52, $P < 0.001$) or a probable physical etiologic factor ($\chi^2$ = 11.29, $P < 0.001$) had a significantly lower risk for schizophrenia than siblings of probands with no identifiable precipitating factor.

Examining in more detail the probable physical precipitating factors, Schulz notes that nearly all the reduction in risk of illness in their siblings, which was only 2.9%, results from probands with head trauma. Furthermore, an intriguing but non-significant relationship was found between the time period from head injury to onset of schizophrenia in the proband and risk for schizophrenia in siblings: <1 year, 1.2%; 2–5 years, 2.9%; > 5 years, 5.6% ($\chi^2$ = 2.28, df = 2, NS).

### Morbid Risk by Premorbid Functioning in Proband

The risk for schizophrenia in relatives of probands with poor school performance was 7.6% and not significantly different from that in the remainder of the series. This suggests that so-called "pfropfschizophrenie" (schizophrenia superimposed on mental retardation) is not, from a familial perspective, distinct from typical schizophrenia. Risk of schizophrenia in siblings was

also not different in siblings of the 27% of probands who were apparently prepsychotically normal (6.8%) vs. the remaining 73% with some premorbid personality disturbance.

### Risk in Siblings of Excluded Probands

Schulz reported that the risk for definite + uncertain schizophrenia in the siblings of the 42 probands he excluded from the main series because of questionable diagnoses was only 2.1%, significantly lower than that found in the siblings of the main proband group ($\chi^2 = 5.97, P = .01$).

The final section of the monograph presents analysis of only the subgroup of cases without apparent precipitating factors. Results, which tended to be similar to those found with the entire cohort, are not reviewed here.

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